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Title page

Title: Comorbidities in Osteoarthritis: A systematic review and meta-analysis of observational studies

Short title: Multimorbidities and Osteoarthritis

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Abstract

Objectives: Osteoarthritis (OA) is a common chronic condition in older people but its association with other chronic conditions is largely unknown. This study aimed to systematically review the literature on comorbidities in people with OA compared to those without.

Methods: We searched four databases for observational studies on comorbidities in people with OA. Studies of OA only or in comparison with non-OA controls were included. Risk of bias and study quality was assessed using the Newcastle-Ottawa Scale (NOS). The prevalence of comorbidities in the OA group and prevalence ratio (PR) and 95% confidence interval (CI) between OA and non-OA groups were calculated.

Results: Forty-two studies from 16 countries (27 case-only and 15 comparative studies) met the inclusion criteria. Mean age of participants varied from 51 to 76 years. Pooled prevalence of any comorbidity was 67% (95%CI: 57%-74%) in people with OA versus 56% (95%CI: 44%-68%) in people without OA. The pooled PR for any comorbidity was 1.21 (95%CI: 1.02-1.45). The PR increased from 0.73 (95%CI: 0.43-1.25) for one comorbidity, to 1.58 (95%CI: 1.03-2.42) for two, and 1.94 (95%CI 1.45- 2.59) for three or more comorbidities. The key comorbidities associated with OA were stroke (PR 2.61; 95%CI: 2.13-3.21), peptic ulcer (PR 2.36; 95%CI: 1.71-3.27) and metabolic syndrome (PR 1.94; 95%CI 1.21-3.12).

Conclusions: People with OA are more likely to have other chronic conditions. The association is dose-dependent in terms of the number of comorbidities, suggesting multimorbidities. Further studies on the causality of this association and clinical implications are needed.

Systematic review registration PROSPERO 2016: CRD42016038484.

Significance and Innovations

This is the first systematic review of the current literature on comorbidities in OA with an extensive list of the conditions.

The key findings are:

[1] 67% of people with OA have at least one other chronic condition, which is 20% higher than people without OA;

[2] there was a graded effect in terms of the risk of having one, two and three or more comorbidities in people with OA compared to those without;

[3] in people with OA, the systems most likely to be affected by comorbidities are upper gastrointestinal, psychological, cardiovascular and endocrine;

[4] stroke, peptic ulcer and metabolic syndrome are the most common comorbidities

INTRODUCTION

Osteoarthritis (OA) is by far the most common form of arthritis and is a major cause of pain and disability in older people. (1) It is a common complex disorder with multiple genetic, constitutional and environmental risk factors. (2) Presence of multiple chronic conditions in a single person causes higher mortality, increased hospitalization, impaired physical and mental health, worse disease outcome and poorer quality of life. (3,4) Co-existence of chronic conditions with OA is also very common, especially in the later decades of life. (5,6) For example, according to the Centre for Disease Control (CDC, Atlanta), more than 30% of people with diabetes and heart disease have OA. (7)

Most literature on OA comorbidity were published in the last three years. The review articles focused on the distribution and impact of individual chronic condition such as cardio-vascular diseases, diabetes and depression in OA.(8–11) Even though comorbidity was discussed as a concept in the 1960s, it was only in 1996 that a distinct definition was first suggested to differentiate "comorbidity" (implying an index disease with mechanistically linked additional conditions) and "multimorbidity" (implying any co-occurrence of medical conditions) within a person. (12) Comorbidity research in OA is still at a preliminary stage and the evidence is yet to be accumulated.

A systematic review on OA reported worsening of pain and decline in functional activities among people due to the presence of other chronic conditions. (13) Clinically, comorbidities in OA create greater challenges for management. The number and pattern of different comorbid conditions determine the severity and burden in multimorbid patients.(14,15)However , except for shared risk factors such as ageing and obesity, little is known about biological plausibility to explain concurrence of OA and associated comorbidities.(16,17) According to the European League Against Rheumatism (EULAR) and National Institute for Health and Care Excellence (NICE), the diagnosis and management of specific comorbidities and understanding their pattern in OA are important and are recommended for best practice. (18,19) An Arthritis Research UK (ARUK) report on multimorbidity in OA also highlighted the importance of understanding the presence of multiple comorbidities with OA for formulating a 'patient-centred' management plan. (20) This study aimed to systematically review the current literature on the comorbidities in OA, specifically, the risk (prevalence or incidence) of comorbidities in people with OA compared to those without OA.

METHODS

A protocol adhering to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA), 2015 statement was designed and registered online (PROSPERO 2016: CRD42016038484).

Search methods and sources

Electronic searches: MEDLINE, PubMed, EMBASE and Scopus database were used to identify studies conducted in any countries between 01-January-1995 and 31-December-2017. Additionally, "comorbidity in OA" was searched in 'Google scholar' search engine and the first 1000 articles were screened for inclusion. The complete search consisted of: [1] searches for OA (any joint); [2] search for co-morbidities; and [3] searches for observational studies. The three search strategies were then combined using 'AND' to generate citations. The details of the search strategies can be seen in Appendix A1. In addition websites of international societies on arthritis such as EULAR, the American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) were also searched.

(18,21,22) References within systematic reviews and review articles were also read for additional relevant original articles.

Selection criteria

Types of studies: All types of observational studies (with or without a non-OA control) documenting prevalence or incidence, and risk ratio of OA comorbidity were included in the study. We defined 'comorbidity' as presence of any concurrent chronic condition in people with OA (as an index disease).

Participants**:** Studies on people with OA diagnosed by a physician through physical examination or radiographic findings. Exposure: OA was the primary exposure. Outcomes: presence of any comorbidities. Other comparisons: studies comparing prevalence/incidence of comorbidities in OA with non-OA control (comparative) and studies of comorbidities in people with OA (case-only) were included.

According to the above criteria, all studies identified by title and abstract were gathered and duplicates were removed. Potentially relevant articles were selected through initial title and abstract screening by two authors [SS and AS] independently. Any disagreement was discussed with WZ. The full text copies of these relevant articles were then retrieved. We retained articles that studied the prevalence of other chronic conditions in people with OA. Full texts of potentially suitable articles were further screened for inclusion by SS. Disagreement in the screening of full texts was resolved by a third reviewer [WZ]. There was no language limitation. We used Endnote for screening of articles; data extraction was done without using any software.

Quality assessment

One reviewer (SS) independently assessed study quality based on items in the Newcastle Ottawa Scale checklist (NOS).(23) Any concern on quality scoring was decided in consultation with another reviewer [AS or WZ]. The NOS tool has a scoring scale under three sections namely; participant selection and representativeness, comparability of study groups, and assessment of outcome or exposure. The quality score is based on a "star" system (range 0-9 stars for case-control and cohort studies and from 0 to 10 for cross-sectional studies) with a higher score representing better methodological quality.

Data Extraction

A customised data extraction form was used to extract data from each study. For each included study we collected following information: (1) authors and publication year; (2) title and journal; (3) study country and location (urban or rural); (4) study design; (5) sampling method (random or non-random); (6) sample size; (7) sample characteristics such as age and gender; (8) number of conditions included; (9) methods of comorbidity measurement; and (10) prevalence (overall and group specific for each comorbidity).

Outcome

The primary outcome was the risk (prevalence) of comorbidities in people with OA (cases) versus those without OA (controls), and secondary outcomes included the types of comorbidities associated with OA. Risk of having the comorbidity between OA and non-OA controls were estimated through prevalence ratio (PR), separately for all comparative studies and for age and sex matched/adjusted comparative studies. For cohort studies, the prevalence of comorbidities reported at the baseline was included for the estimation. Because in these studies, comorbidity was not reported as the outcome.

Statistical analysis

Descriptive characteristics of the studies are expressed as means/medians and/or frequencies as appropriate depending on the variables. For comorbidity count we used median because of wider variation in the list of the diseases across the studies. Heterogeneity between studies was measured using the I^2 (%) and Q test [p value]. (24,25) Publication bias was assessed using funnel plots and Egger's test with statistical significance being conferred to $P< 0.05$. (26) For heterogeneity, I^2 above 75% was considered as wider heterogeneity, demanding careful interpretation of the findings. (25) Prevalence and prevalence ratio (PR) and 95% confidence intervals (CI) were calculated wherever possible for each comorbidity. The PR was chosen over odds ratio (OR) because that we had prevalence data for both OA cases (exposure) and non-OA controls (non-exposure). In this scenario PR is recommended over OR to minimise the overestimation of the relative risk. (27) For prevalence estimation, subgroup analysis was done according to the study design (cross sectional, case-control and cohort). For PR, however, only one article had different study design from others thus not allowing to perform the subgroup analysis as per the study design. So, for the PR estimation,

subgroup analysis was done as per the (NOS). We used the median NOS score (6) as a cut-off for grouping the studies. In order to remove the impact of age and sex, the association of disease specific and system specific comorbidities analysis was done for all the comparative studies and for "age-sex matched control' comparative studies. The results across different studies were pooled using random effects meta-analysis METAPROP package (28), an additional function of STATA (V15, Stata Corp LP, College Station, TX, USA) (29) and Revman V 5.3. (30)

RESULTS

Search results and study qualities

The initial search yielded 70,014 articles from four databases. After removal of duplicates 48,661 remained, of which 1,091 appeared relevant after title screening. Abstract reading confirmed 56 relevant articles and full text papers which were fully assessed. Forty-two articles met the inclusion criteria (Figure-1). On the quality assessment scale (maximum of 10) for cross sectional studies (n=33), the average score was 5.44 (median=6), and of them, 22 studies (31–52) had 5 stars or more. Five case-control and four cohort studies had an average score of 5.22 (range 0-9), with six studies (6,33,53–56) having five stars or more. (Appendix A2)

Study characteristics

Of the 42 included studies, 15 compared comorbidities between people with OA and those without (comparative studies) whereas 27 examined comorbidities in people with OA only (case-only studies). These included three case-control studies (6,57,58), six cohort studies (53–56,59,60) and 33 cross-sectional studies that explored comorbidity in people with OA (1,5,31–52,61–70) (Table-1). We used the baseline comorbidity information from the cohort studies. Thus, we could calculate prevalence only for the comorbidities. Twelve studies were from the USA (32,34–40,53,57,63,65), nine from the Netherlands (1,33,41–44,54,55,59,60), four from the United Kingdom (6,45,46,66), two each from Finland (47,48), Japan (49,56) and Italy (61,67) and one each from Canada (50), Hong Kong (5), Spain (68), Australia (51), South Korea (52), Germany (31), Turkey (62), India (69), Brazil (70), Iraq (58) and Latin America (64). Twelve studies were community-based (6,40,45,47,49,51–53,55,56,65,66), two were

based on national insurance data (32,57) and 28 were hospital-based studies. Eleven studies collected information on knee OA (5,37,49,52,53,56–58,62,68,69), two were on hip OA (47,63), 14 were on both knee and hip OA (1,6,33,39,41,42,45,54,55,55,60,66,67,71), one each on ankle (35), hand (43) and hip/knee/hand (61). Of 15 comparative studies, 12 had controls minimally matched for age and sex of OA cases. In the included studies OA was diagnosed in the following ways: clinician assessment without radiographic findings (n=24); clinical assessment with radiographic diagnosis (n=13 studies); self-reported physician given diagnosis (n=4) (40,45,51,65); and radiographic findings alone (n=1) (62). Details of the study characteristics are provided in Appendix B1.

The mean age of the study participants varied from 50.8 years to 76.1 years across studies. The sample size of the included studies ranged from 91 to 237,172 (40,49) and included both men and women except one which had only women. (56) The detailed demographic information (age, sex, body mass index and obesity) is provided in Table-1.

Prevalence of comorbidities

Of 42 included studies, 15 case-only studies and 8 comparative studies had data on comorbidity count for analysis. The pooled prevalence of any chronic condition in all studies among people with OA was 66% (95%CI: 58%-74%). In OA cases, 29% of participants had a single comorbidity, 25% had two and 24% had three or more. Further subgroup wise prevalence across the study design is provided in Figure-2. High heterogeneity was observed across studies. Technical details of the data extraction are provided in Appendix A3 and A4.

The leading systems in terms of pooled prevalence in people with OA were cardiovascular (35%), musculoskeletal (34%), neurological (30%) and upper gastrointestinal (UGI) (19%). The leading chronic conditions reported among people with OA were hypertension (50%, 95% CI: 36%-57%), dyslipidaemia (48%, 95% CI: 14%-66%) and back pain (33%, 95% CI: 11% - 37%) followed by thyroid disorder (26%, 95% CI: 6%-68%) and depression (17%, 95% CI: 12%-22%). The proportion of chronic conditions were reported to be higher in case-control and cross-sectional studies compared to cohort studies. (Figure- 3) Details of the prevalence across the study designs are given in Appendix B2 and B3. All the included studies were cross sectional in nature except two.

Comparison between people with and without OA

Forest plots for PR and 95%CI between OA and number of chronic conditions in comparative studies are shown in Figure-4. Eight studies reported the prevalence of comorbidities in people with OA and age and sex matched controls, which were used to estimate PR for matched studies. (6,34,44,45,49,56,64,65)

The pooled PR for any comorbidity in studies matched by age and sex was 1.21 [95% CI: 1.02-1.45, I^2 = 100%, P <0.001]. The PR increased from 0.73 [95% CI: 0.43-1.25] for one comorbidity, to 1.58 [95% CI: 1.03-2.42] for two, and 1.94 [95% CI: 1.45-2.59] for three or more comorbidities in OA compared with non-OA people. [Figure-4] Subgroup analysis was done for the studies according to the NOS score (see Figure-4). Funnel plots for the studies are given in Appendix B4 and Eggers test reported non-significant publication bias (P value = 0.72).

The risks for having system specific comorbidities in age and sex matched/adjusted studies among OA people were significantly high for upper gastro intestinal (UGI) disorder [PR 2.36; 95% CI: 2.31-2.41], psychological conditions [PR 1.75; 95% CI:1.20-2.54], and cardiovascular disease [PR 1.56; 95% CI: 1.34-1.86] compared to non-OA people. For specific diseases the risk of stroke was 2.61 [95% CI: 2.13-3.21] times higher among OA people compared to non-OA, followed by peptic ulcer [PR 2.36; 95% CI: 1.71-3.27] and metabolic syndrome [PR 1.94; 95% CI 1.21-3.12]. [Table 2]

DISCUSSION

To our knowledge, this is the first systematic review of the literature to examine the evidence of an extensive list of comorbidities in OA. Forty-two studies from 16 countries were included. The key findings are: [1] 67% people with OA had at least one other chronic condition, being 20% higher than those without OA; [2] there was a graded effect in terms of the risk of having one, two, and three or more comorbidities in people with OA compared to those without; [3] the systems most likely to be affected by comorbidities in people with OA were upper GI, psychological, cardiovascular and endocrine; and [4] stroke, peptic ulcer and metabolic syndrome were the commonest comorbidities in OA.

Studies on multi-morbidity from both the developed and developing countries reported OA as a leading chronic condition. (14,15,72,73) The risk of having any comorbidities in OA was reported to be 2.35 times more in the UK general practices population (46) and the risk for multimorbidity was three times higher in the Australian population compared to a non-OA group. (51) The stronger association of number of comorbidities in OA indicates the existence of the problem of multimorbidity among these people. Besides the number, pattern of chronic conditions in OA influences management decisions. Comorbidities increase the complexity of care through increased exposure to the medication and other chronic conditions. However, the relationship of these factors with the comorbidities are yet to be discovered. This requires further research to explore the pattern and causality of comorbidities in OA.

However, the risk of developing comorbidities in OA patients and their biological plausibility is not well investigated. Of the 42 studies included, only 12 primarily examined the comorbidity in OA, 15 had a comparative group and 27 were published in the years 2010-2017. This indicates the quality of the evidence and growing interest in OA comorbidity. Evidence on risk of having disease specific comorbidities is not well documented except for hypertension, diabetes and heart diseases and further less reported according to the system. (61) Few studies are available to explain the association. For example, a meta-analysis done by Wang et al on the association of OA with cardiovascular diseases reported an association with RR of 1.24, which is less than in our study. (9) Strong associations with other generalised and localised musculoskeletal conditions appear evident. (74,75) But whether co-existence with respiratory diseases is independent or related was considered inconclusive (76), in contrast to our result. According to Parkinson et al, people with OA are at 1.41 times higher risk of getting diabetes. (77) Nearly one fifth of OA patients have depression (11,78) but previous systematic reviews have been inconclusive about the extent of an association.(11) We report risks of eleven comorbidities among those with OA, which is more comprehensive than any previous study to date.

Exploring factors for comorbidities can be difficult, as OA might share different common risk factors with different diseases. Presence of multiple comorbidities could be explained by ageing: an important risk factor for OA and other chronic conditions. But we found positive associations in age-matched comparative studies. Associations of OA with UGI diseases are well documented and usually attributed to long-term use of analgesics, particularly NSAIDs. (79,80) We found non-uniform recording of symptomatic UGI disorders by the studies,

which necessitates correct diagnosis and reporting among patients with OA. Coexistence of cardiovascular comorbidities could be due to shared risk factors such as obesity and metabolic syndrome. (81,82) Besides those, NSAIDs and impaired physical activities in OA have been reported to increase risks of developing cardio-vascular disease.(82–85)' Still, the causal association between OA and cardio-vascular disease is not well understood and could in part be attributable to genetic linkage. (87,88) For the association of OA with depression, hypothesize that the chronicity of the disease, pain, repeated health care utilization, health expenditure and functional limitation could be the drivers of depression among people having OA, and equally depression can influence pain experience. (78) Endocrine disorders such as hypothyroidism and diabetes could have an association with OA at specific joint sites (89), but lack of joint specific information and endocrine conditions in many studies limits our findings. We did not find fair evidence for musculoskeletal comorbidities in OA, even though reporting of similar age-related changes in other joints (90) or muscle weakness or injury causing biomechanical derangement leading to pain (91). The increased reporting of back pain and migraine among both symptomatic OA and asymptomatic OA patients might reflect multiple regional pain resulting from altered pain physiology and central pain' mechanisms. (92)

Although we estimated the pooled prevalence, this needs careful interpretation owing to the large heterogeneity. However, this is only a systematic review of the current literature. The purpose of this review is to identify a signal for future research, not to confirm the prevalence and the risk ratio. Prevalence reported in epidemiological studies are determined by the study design, sample size, case definition and the diagnostic method. The reported prevalence as per the system and disease indicates the existing burden of other chronic conditions in OA, which might affect care. Most of the chronic conditions are age related, thus understanding their coexistence across the age group could have been helpful. However, because of the limited articles available, we could not perform such subgroup analysis and limited our discussion to the association only. The heterogeneity of the studies and limited research highlights the need for better-quality comorbidity research in OA.

There are several limitations to this study. Firstly, since multi-morbidity/comorbidity in OA is not well indexed in literature databases, we might have omitted some studies. Secondly, heterogeneity in prevalence estimates observed in our review, stemming from diversity of methodologies, might have caused uncertainty of the results. Thirdly, there was ambiguity in disease definitions which creates uncertainty, for example, over whether peptic ulcer, gastritis

and acidity should be considered separate entities. Fourthly, suboptimal information about OA reported in studies made it difficult to differentiate between structural OA and symptomatic OA, and to determine whether associations were linked primarily with structural OA or to pain experience. Similarly, the count of chronic conditions and the definition used varied considerably between studies and might have influenced the estimates. (93) Our comparative groups included any non-OA cases, so the comorbidity pattern might have been different because of selection of comparative/control groups, which needs to be interpreted with caution. Furthermore, unavailability of joint specific OA within comparative studies limited the estimation of joint specific comorbidities. Also, the study compiles data from different study designs thus has limitations in understanding the time sequences of OA with comorbidities. Unfortunately, there were not enough number of studies in each subgroup (one in cohort design) in comparative studies to perform subgroup analysis as per the study design.

In conclusion, people with OA are 1.2 times more likely to have any comorbidity than non-OA controls and 2.5 times more likely to have three or more comorbidities. The comorbidities with the highest increase in risk are stroke, peptic ulcer, hypertension and depression. Further research is needed to determine the causality between OA and these common comorbidities to optimise treatment and develop preventative strategies.

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PATIENT CONSENT: No patients were directly included in the study (only in the primary studies of this review).

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Reference 51-92 are available in appendix A5.

Table 1 Characteristics of included studies

	Comparative studies (OA versus Non-OA)	Case only studies (OA only)
Number of studies	15	27
Total Study Participants	773,592	832,423
Mean age in years [Range]	60.1[50.8-76.1]	63.9[54.1-74.0]
Women% [95% CI]	53.0[35.0-70.0]	63.0[57.0-69.0]
Body Mass Index; mean [Range]	27.3[24.0-29.8]	27.0[22.0-31.3]
(#Number of studies)	(3 studies)	(17 studies)
Obesity prevalence, [95% CI]	53.4[42.7-64.1]	31.9[21.6-42.3]
(#Number of studies)	(7 studies)	(18 studies)
Comorbidities assessed*, Median [IQR]	6[4-24]	13[8-15]
(#Number of studies)	(15 studies)	(27 studies)
OA site		
Knee	5	6
Hip	0	2
Ankle	1	0
Both knee and hip	3	11
Hand	0	1
Any joint	5	6
Hand, Hip and Knee	0	1
Not given	1	0
Methods of comorbidity measurement		
Charlson Comorbidity index	0	2
Chronic Illness Rating Scale	1	3
Simple Count	10	16
Functional comorbidity assessment	1	0
Self-Assessed Comorbidity Questionnaire	0	1
Three methods	0	1
Not mentioned	3	4
Study settings		
Community Based	7	5
Hospital Based	6	22
Insurance data	2	0
Methods of OA diagnosis		
Physician diagnosed	6	18
Self-reported	3	1
Radiographic	1	0
Physician diagnosed and Radiographic	5	8

*Number of comorbidities assessed in the studies; #Information on the variable was available on the number of studies

Table 2 Risk ratio of comorbidities associated with osteoarthritis (comparative studies)

	All studies					'Age-sex matched' Studies				
	Number of Studies	Study Participants (OA)	Study Participants (Non-OA)	Prevalence Ratio [95% CI]	I^2 (%) (P_{heter})	Number of Studies	Study Participants (OA)	Study Participants (Non-OA)	Prevalence Ratio [95% CI]	I^2 (%) (P_{heter})
Systems Involved										
Upper Gastro-Intestinal	3	127943	130021	2.35[2.31-2.40]*	100 [<0.00001]	2	124326	124731	2.36[2.31-2.41]*	100 [<0.00001]
Psychological condition	4	129817	139895	1.67[1.23-2.29]*	98 [<0.00001]	2	124326	124731	1.45[1.01-2.34]*	99 [<0.00001]
Cardiovascular	9	177056	342858	1.57[1.35-1.82]*	99 [<0.00001]	5	167274	168723	1.42[1.41-1.43]*	100 [<0.00001]
Endocrine	5	56125	58496	1.26[1.14-1.39]*	76 [0.002]	3	52257	52662	1.18[1.13-1.23]*	16 [0.30]
Genito-Urinary	2	14992	17070	1.43[0.91-2.25]	96 [<0.00001]	1	11375	11780	1.14[1.07-1.22]*	NA
Musculoskeletal	3	124521	124826	2.20[0.83-5.80]	100 [<0.00001]	3	124521	124826	2.20[0.83-5.80]	100 [<0.00001]
Respiratory Diseases	3	55809	57887	1.11[1.00-1.24]	85 [0.001]	2	52192	52597	1.05[0.96-1.15]	76 [0.04]
Disease specific										
Stroke	2	5491	15164	1.52[1.30-1.79]*	98 [<0.00001]	1	1874	9874	2.61[2.13-3.21]	NA
Peptic Ulcer Disease	2	124326	124371	2.36[1.71-3.27]*	88 [0.004]	2	124326	124371	2.36[1.71-3.27]*	88 [0.004]
Metabolic syndrome	2	316	597	1.60[1.20-2.13]*	1[0.31]	1	65	65	1.94[1.21-3.12]*	NA
Peripheral Vascular Disease	2	124326	124731	1.76[1.04-2.97]*	96 [<0.0001]	2	124326	124731	1.76[1.04-2.97]*	96 [<0.0001]
Depression	4	129817	139895	1.94[1.62-2.32]*	84 [0.0003]	2	124326	124731	1.70[1.29-2.24]*	90 [0.001]
Dyslipidaemia	5	120924	277277	1.45[1.15-1.84]*	97 [<0.0001]	2	113016	113016	1.57[1.55-1.58]*	0 [0.93]
Hypertension	8	165681	331078	1.76[1.44-2.17]*	100 [<0.0001]	4	155899	156943	1.55[1.26-2.07]*	100 [<0.0001]
COPD/Asthma	3	55809	57887	1.45[1.21-1.74]*	85 [0.001]	2	52192	52597	1.35[1.10-1.66]*	89 [0.003]
Back Pain	2	124326	124731	1.92[1.00-3.66]	99 [<0.0001]	2	124326	124731	1.92[1.00-3.66]	99 [<0.0001]
Coronary Heart Disease	5	131883	143005	1.27[0.69-2.33]	99 [<0.0001]	3	123692	127841	0.98[0.39-2.44]	100 [<0.0001]
Diabetes	4	44750	46716	1.17[1.13-1.21]*	0 [0.55]	2	40882	40882	1.25[0.87-1.78]	26 [0.25]
Neoplasm	2	14992	17070	2.08[0.47-9.18]	99 [<0.0001]	1	11375	11780	0.98[0.87-1.10]	NA

*P Value<0.05 ; P_{heter} – P value for heterogeneity test

NA- Not Applicable; COPD: Chronic Obstructive Pulmonary Diseases

Figure legends

Figure-1 PRISMA Flow of study selection

Figure 2 Prevalence of number of any comorbidities in people with OA across the study design

Figure 3 Prevalence of comorbidities in people with OA (disease and system specific)

Figure-4 Risk of having comorbidities among people with Osteoarthritis compared to people without Osteoarthritis

Figure-1: PRISMA Flow of study selection

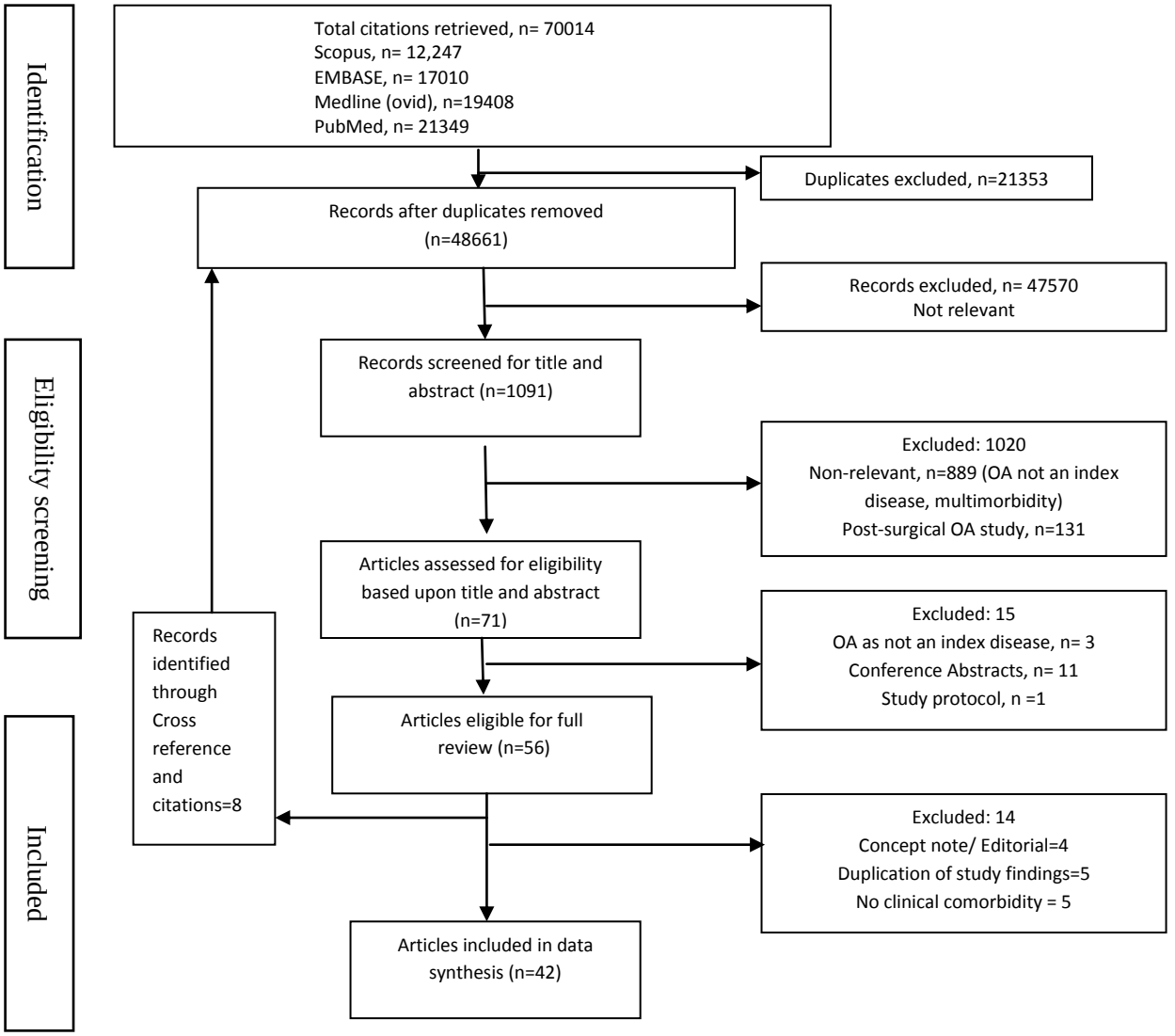
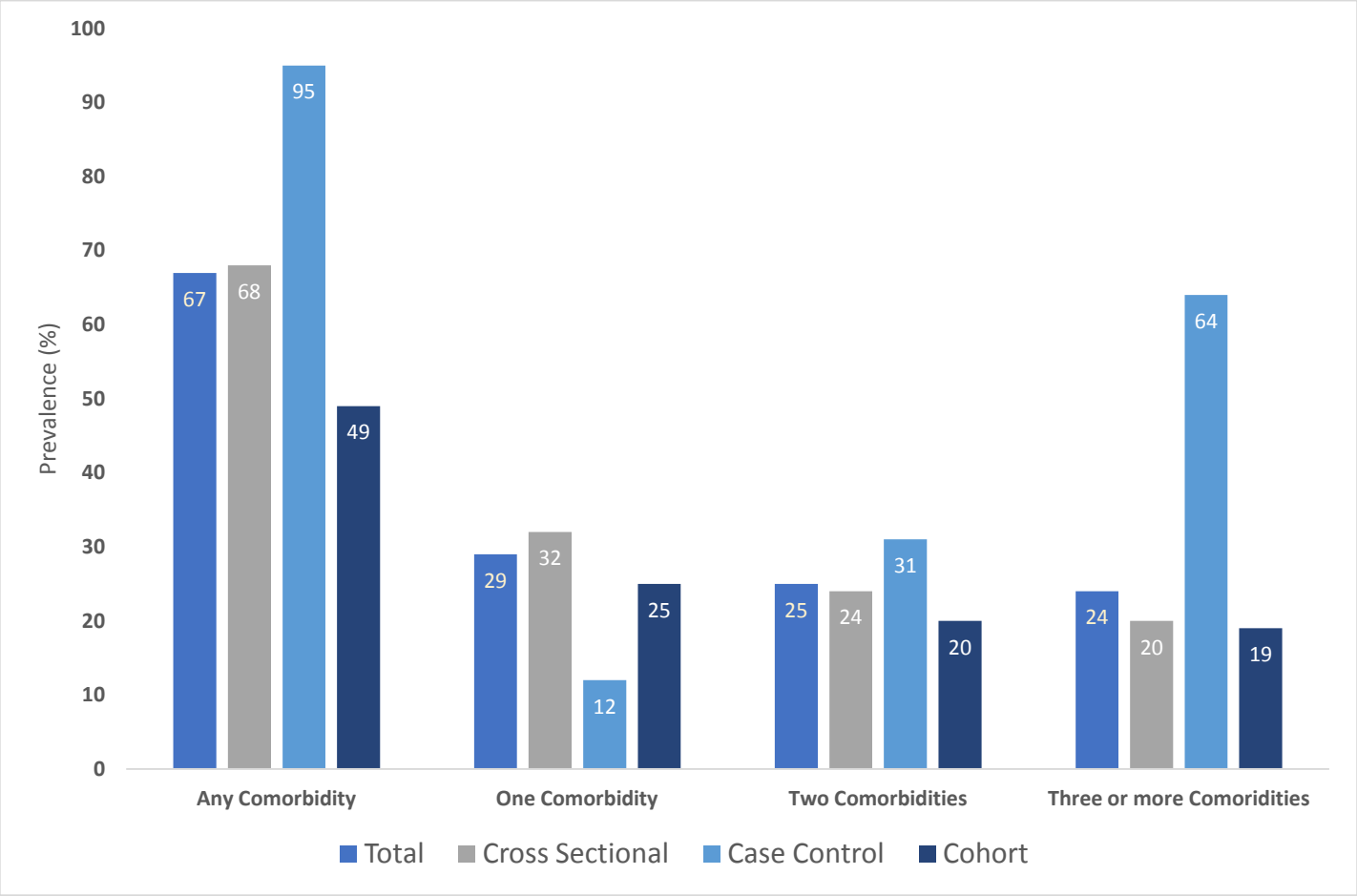
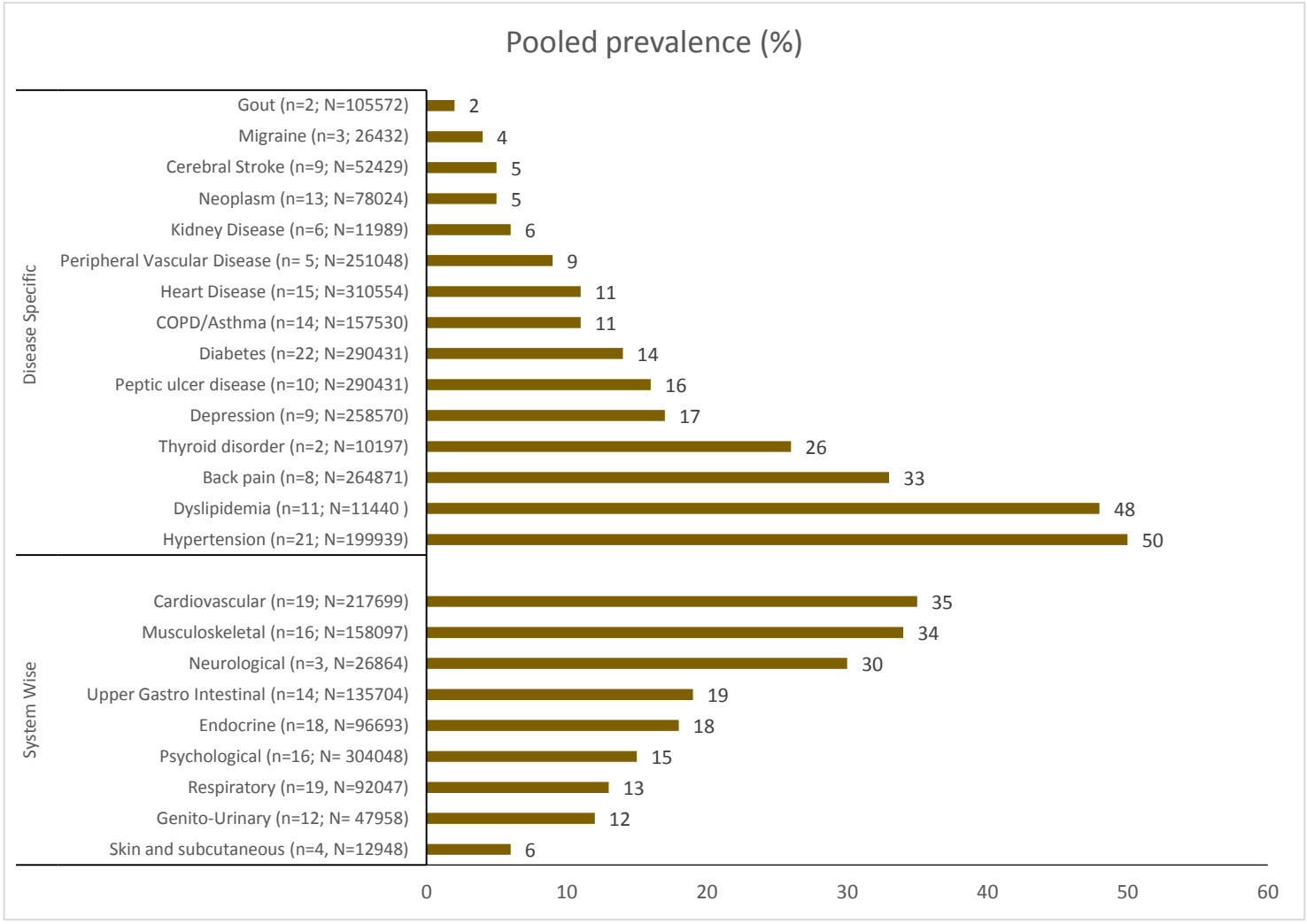


Figure 2 Prevalence of number of any comorbidities in people with OA across the study design



[Number of studies in each group; Any comorbidity – Total (21), Cross sectional (16), case control (1), cohort (4); One comorbidity- Total (18), Cross sectional (13), case control (2), cohort (3); Two comorbidities- Total (16), Cross sectional (12), case control (2), cohort (2); Three comorbidities- Total (14), Cross sectional (10), case control (2), cohort (2)]

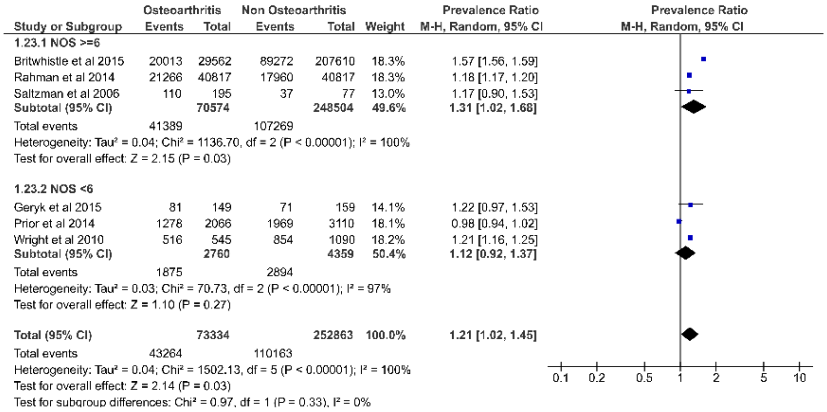
Figure 3 Prevalence (%) of comorbidities in people with OA (disease and system specific)



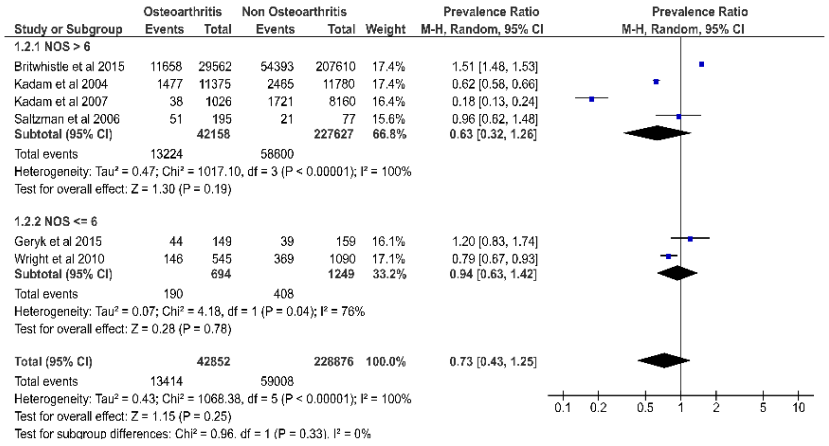
(n=Number of studies, N= Number of participants; COPD- Chronic Obstructive Pulmonary Diseases)

Figure-4 : Risk of having comorbidites among people with Osteoarthritis compared to people without Osteoarthritis

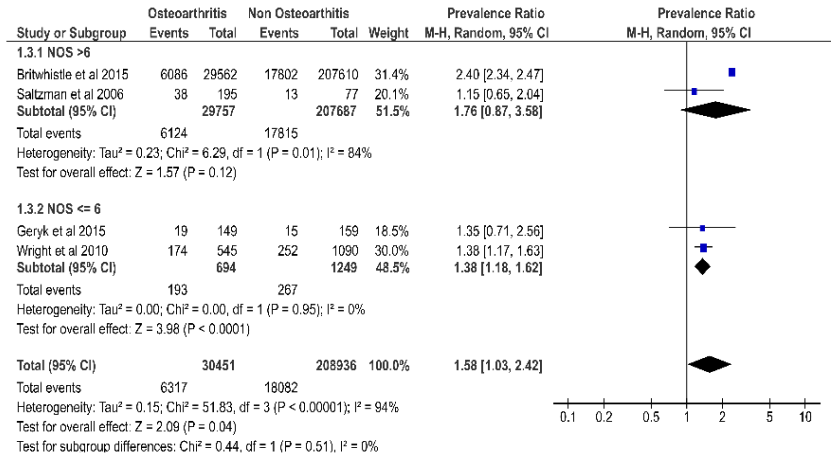
a. Any comorbidity



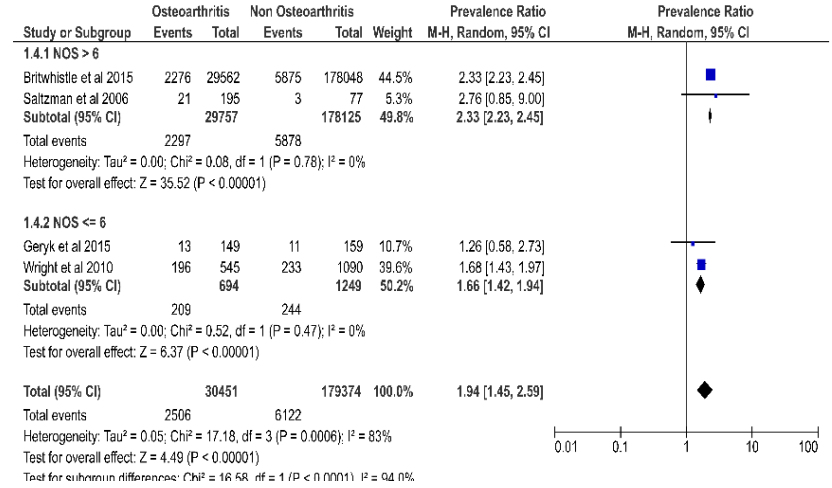
b. Any single comorbidity



c. Any two comorbidities



d. Any three cmorbidities



#Only systemic comorbidities information has been used from the study by Saltzman et al 2006 in all estimates; NOS- Newcastle Ottawa Scale; M-H Mantel